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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,510	05/26/2000	MICHAEL TSCHOPE	P100564-0000	7619

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EXAMINER
PRASAD, SARADA C

ART UNIT	PAPER NUMBER
1646	13

DATE MAILED: 01/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/508,510	TSCHOPE ET AL.1034	
	Examiner	Art Unit	
	Sarada C Prasad	1646	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23, 25-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

1. Applicant's election with traverse of Group I (claims 1-15 and 18-26) in Paper No. 12 (11/02/01) is acknowledged. As per Applicants' request in Paper No.10 (10/1/01), claim 24 is cancelled, and currently claims 1-23, 25-26 are pending.

The traversal is on the ground(s) that the presence of one or several amino acids is an essential feature of the invention, and restricting of instant claims into Groups I and II based on the presence of methionine in claims 16-17 is not appropriate. Applicants' argument has been found to be persuasive and the Restriction Requirement is therefore withdrawn. Currently claims 1-23, and 25-26 are under consideration.

Specification

2a. Instant specification is objected to because it lacks division of the application into distinct sections as required.
Appropriate correction requested.

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
1. Field of the Invention.

2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

Objections to claims:

2b. Claim 19 is objected to because it does not end with a period.

Claim Rejections - 35 USC § 112-Second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-23, 25-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3a. Claims 13 is vague and indefinite reciting 'chemical integrity' because it is not clear as to what is meant by 'chemical integrity'.

3b. Claim 14 and 26 are vague and indefinite in reciting 'physical integrity' because it is not clear as to what is meant by 'physical integrity'.

3c. Claim 18 and 26 are vague and indefinite in reciting 'auxiliaries' in referring to the components for adjusting the tonicity. It is not clear as to what is not included and included by the term "auxiliaries".

3d. Claims 1-3 are vague and indefinite because the phrase 'as active ingredient' is missing the article ('an' or 'the'), and which is the biological activity being referred to if the article 'an'.

Additionally, the standard terminology for representation of units of IFN-β is 25 x 10^6 U/ml instead of 25 MU/ml as recited in the instant claim.

3e. Claim 20 is vague and indefinite in reciting 'physiologically acceptable preservatives'. It is not clear if it is required to include more than one preservative or whether a single preservative would meet the limitations of he claim.

3f. Claim 26 is vague and indefinite in reciting 'or/and' because in each case the limitations that follow the use of the phrase 'or/and' are not clear for example, "A and/or B and/or C" or "A and (B and/or C)".

3g. Claim 5 is vague and indefinite in reciting 'originates from CHO cells', because it is not clear how human IFN-β originates from CHO cells. This rejection can be obviated by reciting 'IFN-β recombinantly produced in CHO cells'.

3h. Recitation in claim 6 of ' a concentration of 10 mM/l to 1 mol/l' is indefinite because it is not clear as to what is the buffer constituent, such as 'phosphate or acetate' that is present at the said concentration.

3i. Claim 23 is indefinite because it is not clear if recitation of 'unit doses' is meant as an additional element, or is it intended as 'packaged in unit doses of 1-25 x 10^6 IU'

3j. Claims 25 is indefinite because the only required step is a negative limitation and involves no process steps. Therefore, the claim is incomplete.

Additionally, 'using a formulation' is not 'a process for improving the shelf life' and use of the term 'using' is indefinite because it is not a method step.

3k. Use of parenthesis in claim language make claim 26 indefinite because it is not clear if the parenthetical phrase 'is' or 'is not' a limitation.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4a. Claims 1-17, 21-23, and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,151,265 (1992), in view of U.S. Patent No. 5,358,708 (10/25/1994).

U.S. Patent No. 5,151,265 (1992) teaches a liquid pharmaceutical composition of non-lyophilized IFN-γ, or recombinant IFN-γ including a buffer capable of maintaining the pH of the liquid composition within the pH range of 4.0-6.0 (abstract, lines 1-6). The formulation contained 5x 10^6 U/ml (column 3, Example 1, lines 1-2, column 4, 2nd para lines 1-2) of the cytokine, and was stable for prolonged periods when stored at –20°C to 30° C with the preferred storage temperature in the range of 2-8°C (column 3, entire 4th para), in succinate buffer and mannitol as the stabilizing agents (claim 15). U.S. Patent No. 5,151,265 also disclosed that the shelf life was better in the absence of human serum albumin (Table 1, column 4), thus meeting

all of the limitations of instant claims 1. U.S. Patent No. 5,151,265 also teaches liquid pharmaceutical compositions of recombinant IFN-γ, which meets the limitations of instant claims 21-23.

However, U.S. Patent No. 5,151,265 prepared stabilized formulation of IFN-γ and not of IFN-β as in instant claim 1; did not teach use of buffer to maintain a pH range close to neutral 6-7.2 as in instant claim 2, nor did it teach inclusion of amino acids as recited in instant claim 3.

On the other hand, U.S. Patent No. 5,358,708 teaches incorporation of methionine, histidine, or mixtures thereof in order to increase the stability of aqueous formulations comprising GM-CSF, or an interleukin (claims 1-12). U.S. Patent No. 5,358,708 also discloses several approaches taken to stabilize, and prepare protein formulations of IFN-α, erythropoietin, human plasminogen, IL-2, and plasmin (column 1, paragraphs 3-7). In particular, disclosure of U.S. Patent No. 5,358,708 also points out that their invention can be used 'to stabilize all of the proteins in the IFN family produced in the human body, including related, or recombinant proteins, which confer resistance to viral infection, affect proliferation of cells and modulate the response of the immune system' including IFN-β (column 2, detailed description of the invention, lines 44-58).

Therefore, in light of the combined teachings of U.S. Patent No. 5,151,265, U.S. Patent No. 5,358,708, it would have been prima facie obvious to one of skill in the art, at the time the invention was made, to prepare stabilized formulations of non-lyophilized IFN-β at a concentration of up to 25 x 10^6 U/ml , in the absence of human serum albumin, maintaining pH close to neutral (5-8 as in claim 1, or a more narrow range of 6.0-7.2 as in claim 2), while retaining biological activity and chemical/physical integrity when stored for prolonged periods at

25 ^{0}C, thus rendering instant claims 1, 2, 4-14 obvious. It would also have been prima facie obvious to one of ordinary skill in the art to have includes the amino acid, methionine, as a stabilizing agent as taught by U.S. Patent No. 5,358,708 in preparing the stabilized formations of IFN-β thus rendering instant claims 1-17, 21-23, 25-26 obvious.

The motivation is provided by the need to stabilize IFN-β as needed for therapeutic purposes for administration as is. Reasonable expectation of success was also provided by the knowledge that pH near neutral would be beneficial in order to administer the formulations directly to the patients, because the pH of body fluids is close to neutral. Such use of IFN-β formulations that do not require expensive lyophilization step, have no contamination with other extraneous proteins which make protein stability testing questionable, and have stability over prolonged periods would be also be economically beneficial.

Conclusion

5. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday – Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
January 8th, 2002